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REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 9-11, 13, 21, 38, and 40-52 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

For the examiner's convenience in examination, the organization of the new and amended claims is as follows:

Claim 40 is now the main claim defining (A) a peptide comprising solely hydrophobic and positively charged amino acids, wherein at least one but not all of the amino acids are D-amino acids, with the limitations set forth in the claim but without defining that the peptide is cytolytic but not hemolytic; (B) a peptide comprising hydrophobic, positively charged and polar amino acids, wherein at least one but not all of the amino acids are D-amino acids, with the limitations set forth in the claim but without defining that the peptide is cytolytic but not hemolytic; (C) a random copolymer consisting of a hydrophobic, a positively charged and a D-amino acid, with the limitations set forth in the claim but without defining that the peptide is cytolytic but

not hemolytic; and (D) a mixture of peptides defined by the process.

Claim 10 is dependent on claim 40 and defines characteristics of the peptides.

Claims 41, 9, 11, 42, 13, 43-46 define peptides according to claim 40(A).

Claims 47-49 define peptides according to claim 40(B).

Claims 50 and 21 define peptides/random copolymers according to claim 40(C).

Claims 51-52 define peptides/mixtures according to claim 40(D).

Claim 38 define a composition comprising a peptide according to claim 40.

All the claims are supported by the specification. Support for added definitions/claims can be found in the specification as follows:

(i) the peptides have at least 6 amino acid residues - claim 40 (p. 8, lines 9-10; and previous claim 11)

(ii) mixture of peptides as obtained by the process - claims 40(D), 51, 52 (p. 8, lines 21-26; p. 50, example 8);

(iii) claims 45-46 - Lys/Val peptides (example 4, p. 44)

Claims 27-29 have been rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. While applicants do not concede to the examiner's position, this rejection is made moot by the cancellation of claims 27-29 without prejudice.

Claims 8-13, 37, and 39 have been rejected under 35 U.S.C. §112, first paragraph, as lacking written description. The examiner states that each of the cited claims is drawn to a genus which encompasses peptides in which all of the amino acids are of the D-configuration and that there is no descriptive support for such a genus. This rejection is obviated by the cancellation of rejected claims 8, 12, 37 and 39 without prejudice and the amendment of claims 9-11 and 13 to be dependent from claim 40 or 41, which include the feature that the amino acids in the non-natural synthetic peptide cannot be all D-amino acid residues.

Claims 1, 6, 81-3, 20, 21, 27-29, 35, and 37-39 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

Insofar as claims 1, 8, 12, and 39, and claims dependent therefrom, are concerned, the indefiniteness issue is made moot by the cancellation without prejudice of the rejected claims even though applicants do not agree with the

examiner's comments. New claim 40 however recites that "the peptide has a ratio of hydrophobic to positively changed amino acids such that the peptide is cytolytic to pathogenic cells but does not cause cytolysis of red blood cells", which is an important property of the peptides according to the present invention. As supported in the specification at page 10, lines 3-9, peptides with a suitable hydrophobic to positively charged amino acid ratio can be readily screened with the antibacterial and hemolytic tests disclosed in the specification.

Regarding claim 21, this part of the rejection is obviated by the amendment to claim 21 to make clear that the recited ratio is a molar ratio and that the recited Lys and first Leu residues have the L-configuration.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 8-11 have been rejected under 35 U.S.C. §102(a) as being anticipated by Shai, *J. Biol. Chem.* 271:7305 (1996). Although applicants do not agree with the examiner's reasoning, this issue is made moot by the cancellation of rejected claim 8. Claims 9-11 are amended to depend from new claim 40 or 41, which would not be subject to this rejection,

Shai for this reason. This ground of rejection is in addition to the § 102 rejection above. The examiner has further added that this rejection is directed to close structural homologs of SEQ ID NOS:1, 12 and 14, and that as indicated in the previous Office Action, "a peptide biochemist of ordinary skill would have expected that if the side chain of a single amino acid were extended or reduced by one methylene unit, the result would be a peptide with substantially the same activity as was observed before the modification [*In re Shetty* (195 USPQ 753) and *In re Hass and Susie* (60 USPQ 544)]". Setting aside the issue of "D" versus "L" configuration, the peptide disclosed in Shai is the following, wherein X is phenylalanine:

GFXALIPKIISSPLFKTLLSAVGSALSSSSGGQE$(NH_2)_2$

Thus, according to the examiner, a peptide biochemist of ordinary skill would expect substantially the same antibacterial activity for the peptide in which X is phenylalanine as would be observed for the otherwise identical peptide in which X is phenethylglycine. The previous argument that these peptides are excluded because Shai peptides occur in nature and are excluded anyway, were not found persuasive by the examiner because one of the amino acids in the Shai's peptides is not naturally occurring. Thus, the examiner takes

the position that the claims are rendered obvious. This rejection is respectfully traversed.

With due respect to the examiner, the examiner's reasoning here is just plain wrong. Shai discloses pardaxin peptides containing different hydrophobic, positively charged and polar amino acids and a residue H_2N-CH(CH_2-CH_2-COX)COX wherein X is ethylenediamine. However, contrary to the examiner's assertion, this residue is **not** an amino acid at all and therefore cannot be an amino acid not occurring in nature. While this compound can be designated a chemical derivative of a natural amino acid, no peptide biochemist would regard this compound as being encompassed within the definition of an amino acid. In fact, this same question was posed to several biochemists, including Prof. Shai, a co-inventor of the instant application and a biochemist recognized as an expert in the area of peptide biochemistry and author or co-author of innumerable scientific publications, and the response was unanimous - this is clearly not an amino acid.

Claims 1, 27-29, and 39 are now cancelled without prejudice. New claim 40 corresponds to cancelled claim 1. It is applicants' position that Shai does not teach or suggest a peptide as defined in claim 40 (A) or (B), namely, "a non-natural synthetic peptide having at least 6 amino acid

particularly in view of the proviso excluding SEQ ID NOs:1, 12 and 14.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 8-12, 20-21, 27-29, and 38 have been rejected under 35 U.S.C. §102(e) as being anticipated by Maloy, U.S. Patent 5,792,831. This rejection is now obviated for the reasons discussed below.

The examiner states that Maloy teaches cytolytic peptides containing D-amino acids that are not hemolytic. However, more accurately, Maloy discloses peptides in which all amino acids (except glycine) are D-amino acids. Claims 1 and 20 were said by the examiner to be anticipated because the peptide disclosed by Maloy at col 27, line 10+ consists of leucine and lysine residues in which the leucine residue fulfills the roles of both hydrophobic and D-amino acids and the lysine residue fulfills the roles of both positively charged and D-amino acids. This part of the rejection is obviated by the cancellation of claims 1 and 20 without prejudice. New claims 40, 41 and 47 now explicitly exclude the possibility that all amino acids are D-amino acid residues, and are thus not subject to this anticipation rejection.

Regarding claim 20, the examiner held that it is anticipated by Maloy's peptide of SEQ ID NO:9 because the amino acids D-lysine, D-leucine and D-leucine are present in a 2:1:1 ratio. Applicants believe that perhaps the examiner had intended to refer instead to claim 21. Claim 21 is now amended to indicate that the lysine and first leucine are L-amino acids, and this part of the rejection is now moot. The examiner held that claim 12 is anticipated by Maloy's peptide of SEQ ID NO:9 because this is a 12-mer peptide in which at least 1/3 of the amino acids are of the D-configuration. In fact, all the amino acids in Maloy's peptide of SEQ ID NO:9 are of the D-configuration. Claim 12 is now cancelled and the corresponding new claim 42 excludes peptides in which all the amino acids are of the D-configuration, thereby obviating this part of the rejection.

According to the examiner, claims 8-13, 37, 39 permit all of the amino acids of the peptide to be of the D-configuration, and claim 1 permits all of the chiral amino acids to be of the D-configuration, as long as an alpha-helix breaker moiety, such as glycine, is present (see the instant specification, p.5, line 29). The examiner asserts that many of the peptides disclosed by Maloy contain an alpha-helix breaker moiety and, as such, meet the requirements of claim 1.

residues and a net positive charge which is greater than +1, said peptide comprising hydrophobic, positively charged and optionally polar amino acid residues, wherein at least one but not all of such amino acid residues is a D-amino acid, said peptide having a ratio of hydrophobic to positively charged amino acids such that the peptide is cytolytic to pathogenic cells but does not cause cytolysis of red blood cells." Thus, the peptides of claim 40 and the composition of claim 38 are not obvious over Shai.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claim 39 was rejected under 35 U.S.C. § 103 as being unpatentable over Maloy (US 5,792,831). According to the examiner, while Maloy does not disclose a mixture of two or more peptides, the examiner takes the position that it would have been obvious to one of ordinary skill to combine two peptides for additive effects.

This rejection is obviated by the cancellation of claim 39 without prejudice because the intention was not to make a simple mixture of two or more peptides, but to prepare a mixture of a plurality of peptides by solid phase synthesis. Such a mixture is now defined in claims 40(D) and 51 as a "product-by-process".

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 8-11, and 27-29 were rejected under 35 U.S.C. §103 as being unpatentable over Paradies, US Patent 4,874,850.

Paradies discloses pharmaceutical preparations made up of a micelle or a vesicle each consisting of a cationic tenside with a monovalent ion and a hydrophobic cyclic or linear peptide. In the description of the state of the art in col. 47, line 59, it is mentioned that tuftsin is not hemolytic. In col. 69, Fig. 6, the sequences of tuftsin and analogs thereof are disclosed, one of them having a D-Pro residue of the sequence: L-Thr-L-Lys-D-Pro-L-Arg.

According to the examiner, this rejection is based on the examiner's assertion that each of the following peptides would have been obvious to the peptide chemist of ordinary skill: Thr-Orn-D-Pro-Arg (Orn is ornithine) and Thr-Apg-D-Pro-Arg (Apg is aminopentylglycine). It is the examiner's position that a peptide biochemist of ordinary skill in the art would have expected, *a priori*, that these two last peptides would have the same activity as the peptide with lysine. This rejection is respectfully traversed.

bacteriostatic in their inhibitory effect and do not result in cytolysis of pathogenic cells. There is simply no implication from Paradies' disclosure that the peptides of Paradies are cytolytic. Accordingly, Paradies does not make obvious the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 8-11, 27-29, 38 and 39 were rejected under 35 U.S.C. §103 as being unpatentable over Jacob, US Patent 5,635,479. The examiner holds that Jacob discloses magainin peptides for treatment of cancer including the peptides of SEQ ID NOS: 115 and 117, that are all-D peptides, except for the glycine residue, and thus these peptides meet the limitation of a peptide containing an alpha-helix breaker moiety.

This rejection is obviated by the cancellation without of prejudice rejected claims 1, 8, 27-29 and 39. The present claims exclude peptides in which there are no L-amino acids since the claims positively recite that not all amino acid residues can be D-amino acids. Accordingly, Jacob cannot lead one of ordinary skill in the art to the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

containing two D-amino acids and a charge greater than +1. It is not disclosed in Paradies that gramicidin is cytolytic, but the examiner states that if it is cytotoxic to microorganisms, it is cytolytic. In addition, the examiner holds that there is no evidence that if the D-amino acids in gramicidin S were replaced by L-amino acids, the result would be a peptide that is found in nature. Accordingly, the examiner states that the disclosed gramicidin meets the limitations of the claims, and the claims are rendered obvious. This rejection is respectfully traversed.

First, it appears to applicants that the examiner's reasoning would lead more properly to an anticipation rejection rather than an obviousness rejection. The rejected claims 1, 8 and 27-29 are now cancelled in favor of the new claims and the dependency of claims 9-11 and 38 is changed, thereby obviating this rejection. The feature in the presently claimed invention of the peptide having "a ratio of hydrophobic to positively charged amino acids such that the peptide is cytolytic to pathogenic cells but does not cause cytolysis of red blood cells" is not disclosed or taught in Paradies. Disclosure that peptides inhibit the "growth" of pathogenic cells in no way suggests that the inhibition occurs through cytolysis. In fact, many antibiotics are